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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MATHIAS C. ZOHOUNGBOGBO,
Appellant

Appeal 2008-5274
Application 09/982,554[1]
Technology Center 1600

Decided[2]: February 12, 2009

Before CAROL A. SPIEGEL, DONALD E. ADAMS, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

SPIEGEL, *Administrative Patent Judge*.

DECISION ON APPEAL

I. Statement of the Case

This is an appeal under 35 U.S.C. § 134 from an Examiner's final rejection of claims 45-47, 49-52, and 54-56. The Examiner has withdrawn

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[1] Application 09/982,554 ("the 554 application"), filed 18 October 2001, is a continuation-in-part of application 09/333,097, filed 15 June 1999, and of application 09/225,819, filed 5 January 1999, which claims priority under 35 U.S.C. § 119 of European Patent Applications 98830365.7 and 99201794.7, filed 16 June 1998 and 4 June 1999, respectively. The real party in interest is Mathias Christian Zohoungbogbo (Appeal Brief, filed 13 November 2007 ("Br."), 2).

[2] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 CFR § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

the final rejection of claims 48 and 53, only other pending claims (Ans.[3] 3). We have jurisdiction under 35 U.S.C. § 134(a). We AFFIRM, but denominate our affirmance as a NEW GROUND OF REJECTION.

The subject matter on appeal is directed to a method of treating a person on a ketogenic diet to reduce the amount of cholesterol, triglycerides, glucose, uric acid, transaminases, and fibrinogen in the person's body. Claims 45 and 46 are illustrative and read (Br. 29-30, Claims App'x):

> 45. A method for treating persons subjected to a ketogenic diet, so as to reduce the concentration of the body chemicals cholesterol, triglycerides, glicemia [sic], uric acid, transaminases and fibrinogen said method comprising the step of:
>
> administering a composition of a plurality of agents including;
>
> a hypocholesterolemic agent, wherein said hypocholesterolemic agent is selected from the group consisting of benfluorex, which is present in the amount from 7% to 23% in weight of the total amount of the composition and ursodesoxycholic acid which is present in the amount from 14% to 17% in weight of the total amount of the composition;
>
> a hypotriglyceride agent, wherein said hypotriglyceride agent is benfluorex which is present in the amount from 7% to 23% in weight of the total amount of the composition;
>
> a lipasic and proteasic agent, wherein said lipasic and proteasic agent is pancreatin IX F.U. which is present in the amount from 27% to 43% in weight of the total amount of the composition;
>
> a hypoglycemic agent, wherein said hypoglycemic agent is metformin which is present in the amount of 36% to 41% in weight of the total amount of the composition; and
>
> a hydrocholeretic agent, wherein said hydrocholerectic agent is selected from the group consisting of Na dehydrocholate which is present in an amount from 9% to 14%

[3] Examiner's Answer mailed 7 February 2008.

> in weight of the total amount of the composition and ursodesoxycholic acid which is present in the amount of from 14% to 17% in weight of the total amount of the composition.
>
> 46. The method as claimed in claim 45, wherein in said administration of said composition, said composition further comprises at least one of:
>
> a hypouricemic agent, wherein said hypouricemic agent is centalla asiatica purified triterpenes;
>
> a radical scavenger agent, wherein said radical scavenger agent is selenium;
>
> a sympatholytic agent, wherein said sympatholytic agent is yohimbine;
>
> a sympathicomimetic agent, wherein said symphathicomimetic agent is from the group consisting of phendimetrazine bitartrate and phendimetrazium pamoate; and
>
> at least one vitamin, wherein said at least one vitamin being selected from the group consisting of vitamin A, vitamin B1, vitamin B6, vitamin E and Vitamin [sic] C.

The Examiner rejected claims 45, 47, 49, 50, 52, and 54-56 as unpatentable under 35 U.S.C. § 103(a) over Marquie,[4] Pentikainen,[5] and Poupon[6] in view of Spasmo-Canulase[7] and Krause[8] (Ans.[9] 4). The Examiner

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[4] Marquié et al., "Metabolic and Anti-Atherogenic Effects of Long-Term Benfluorex in Dyslipidemic Insulin-Resistant Sand Rats (*Psammomys obesus*)," *Life Sciences*, 63 (1998): 65-76 ("Marquie").

[5] Pentikäinen et al., "Cholesterol Lowering Effect of Metformin in Combined Hyperlipidemia: Placebo Controlled Double Blind Trial," *Annals of Medicine*, 22 (1990): 307-312 ("Pentikainen").

[6] Poupon et al., "Cholesterol-lowering Effect of Ursodeoxycholic Acid in Patients with Primary Biliary Cirrhosis," *Heptalogy*, 17 (1993): 577-582 ("Poupon").

[7] SPASMO-CANULASE® BITAB® Product Insert, Updated May 2000, downloaded from http://home.intekom.com/pharm/novartis/spasmo_c.html, on 8 January 2003 ("Spasmo-Canulase").

rejected claims 46 and 51 as unpatentable under 35 U.S.C. § 103(a) over Marquie, Pentikainen, and Poupon in view of Spasmo-Canulase and Krause and further in view of Hydrocotyle,[10] Kang,[11] Pondimin,[12] and Keown[13] (Ans. 7).

Appellant has argued the patentability of two groups of claims – Group I: claims 45, 50, 55, and 56 and Group II: claims 46-49, and 51-54 (Br. 15). Therefore, we decide this appeal on the basis of claims 45 and 46. 37 C.F.R. § 41.37(c)(1)(vii).

Appellant essentially contends that the Examiner used hindsight to pick and choose which active agents disclosed in the applied prior art would have been obvious to combine into a single composition for treatment of persons on a ketogenic diet as recited in method claims 45 and 46 (Br. 15-25 and 25-28).

II. Findings of Fact ("FF")

A. Appellant's application

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[8] FOOD, NUTRITION, AND DIET THERAPY: A TEXTBOOK OF NUTRIONAL CARE, seventh edition, Krause and Mahan, 656-658 W.B. Saunders Company, Philadelphia (1984) ("Krause").
[9] Examiner's Answer mailed 7 February 2008 ("Ans.").
[10] "Hydrocotyle," A MODERN HERBAL, Botantical.com Home Page, Electric Newt © 1995, downloaded from http://www.botanical.com/botanical/mgmh/h/hydcol46.html on 8 January 2003.
[11] Kang et al., "Effect of Diet Induced Hypercholesterolemia and Selenium Supplementation on Nitric Oxide Synthase Activity," *Archives of Physiology and Biochemistry*, Vol. 105, 603-607 (1997) ("Kang").
[12] Pondimin® Tablets, PHYSICIANS' DESK REFERENCE (1996): 2066-2067 ("Pondimin").
[13] International Patent Application WO 95/11034, *Composition for Weight Reduction Containing Ephedrine and a Mineral Salt or Chelate*, by Keown et al., published 27 April 1995 ("Keown").

[1] According to the 554 specification ("Spec."), a ketogenic diet may result in certain side effects, e.g., elevated uric acid, glucose, cholesterol, and triglyceride levels in a subject as well as hepatic-pancreatic alterations and mental disorders (Spec. 3).

[2] In part, the 554 specification discloses a pharmaceutical composition for preventing or treating the possible side effects of a ketogenic diet (Spec. 8).

[3] In one embodiment described in Example 8, the pharmaceutical composition is gelatin capsule containing an admixture of

20 mg	diethylpropione chlorohydrate
4 mg	fenfluramine
50 mg	benfluorex
0.4 mg	triiodotiracetic acid
120 mg	pancreatine IX F.U.
200 mg	metformin
40 mg	Na dehydrocolate

and suitable excipients (Spec. 23-24).

[4] According to the specification, diethylproprione chlorohydrate and fenfluramine are anorectic agents; triiodotiracetic acid is a lipolytic agent; benfluorex is a both hypocholesterolemic and a hypotriglyceridic agent; pancreatine IX F.U. is lyophilized pancrease, i.e., a lipasic and proteasic agent; metformine is a hypoglycemic agent; and, Na dehydrocolate is a hydrocoleretic agent (Spec. 6-9 and 12-13).

B. The applied prior art

[5] Krause discloses that a ketogenic diet is extremely low in carbohydrate and high in fat, i.e., fat content provides 80 to 90 percent

of the calories and that serum cholesterol levels are frequently elevated with a traditional ketogenic diet (Krause 657).

[6] Marquie discloses that benfluorex, in addition to producing a significant antidiabetic effect, improves dyslipidemia in sand rats fed a high cholesterol diet (Marquie 74). In other words, benfluorex decreased plasma cholesterol, triglyceride, and insulin levels and improved glucose tolerance in sand rats fed a high cholesterol diet and may help protect against the long term development of atherosclerosis in insulin-resistant diabetes and related conditions (Marquie 75).

[7] Pentikainen discloses that metformin is known to lower blood glucose levels in the treatment of non-insulin dependent diabetes and reports that metformin also significantly lowers concentrations of total cholesterol and LDL-cholesterol while leaving concentrations of HDL-cholesterol and total triglycerides unchanged (Pentikainen 307 and 311). Pentikainen further discloses that minor gastroinstestinal side effects, mainly malaise, pains, meteroism, and loose stools, were common in patients treated with metformin (Pentikainen 311- 312).

[8] Poupon discloses that long term therapy with ursodeoxycholic acid lowers cholesterol levels in both cirrhotic and noncirrhotic patients with PBC (primary biliary cirrhosis), mainly by lowering LDL and VLDL cholesterol while leaving concentrations of HDL cholesterol, total triglycerides, and phospholipids unchanged (Poupon 577 and 581).

[9] Spasmo-Canulase is an antispasmodic composition containing methixene hydrochloride, dimethylpolysiloxane, cellulose, pepsin, glutamic acid hydrochloride, pancreatin, and Na dehydrocholate used

to treat abdominal cramps associated with flatulence (Spasmo-Canulase 1).

[10] Hydrocotyle asiatica is a plant valued for its diuretic properties which acts as a stimulant in small doses and as a narcotic in large doses (Hydrocotyle 1).

[11] Kang discloses that selenium supplemented animals on a high fat diet showed a significant reduction in serum cholesterol compared to control animals on a high fat diet (Kang abstract; 605).

[12] Pondimin is a brand of fenfluramine hydrochloride and one study of normal males has been shown podimin to increase glucose utilization, resulting in decreased blood glucose levels (Pondimin 2066, "Clinical Pharmacology").

[13] Keown discloses a composition comprising a combination of a sympathomimetic agent, e.g., epinephrine or yohimbine, and a salt or chelate of a mineral cation, e.g., chromium or vandanium, which enhances the specific burning of body fat and increases energy expenditure while retarding protein breakdown or lowering cholesterol levels, increasing lean body mass and muscle development (Keown 8:10-9:22).

III. Discussion

A. Legal principles

A claimed invention is not patentable if it would have been obvious to a person having ordinary skill in the art. 35 U.S.C. § 103(a); *KSR Int'l Co. v. Teleflex, Inc.,* 127 S.Ct. 1727 (2007); *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). Facts relevant to a determination of obviousness include (1) scope and content of the prior art, (2) any differences between

the claimed invention and the prior art, (3) the level of ordinary skill in the art, and (4) relevant objective evidence of obviousness or nonobviousness. *KSR*, 127 S.Ct. at 1734; *Graham*, 383 U.S. at 17.

"The combination of familiar elements according to known methods is likely to be obvious when it does nothing more than yield predictable results." *KSR*, 127 S.Ct. at 1739. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose." *In re Kerkhoven*, 626 F.2d 846, 850 (CCPA 1980). "[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980). *See also In re Reese*, 290 F.2d 839 (CCPA 1961).

B. The Examiner's position

As to claim 45, the Examiner concluded that it would have been obvious to treat the side effects of a ketogenic diet, e.g., elevated serum cholesterol levels, with a combination of agents, i.e., benfluorex, metformin, and ursodesoxycholic acid, known to lower elevated serum cholesterol levels based on the teachings of Krause, Marquie, Pentikainen, and Poupon (Ans. 4-6). The Examiner further concluded that it would have been obvious to incorporate pancreatin and sodium dehydrocholate, as taught by Spasmo-Canulase, into the benflorex/ metformin/ursodesoxycholic acid combination, "[s]ince flatulence and abdominal cramps are the common side effects of metformin" (Ans. 6). The Examiner also concluded that optimizing the amount of each active agent in the combination would have within ordinary skill in the art (Ans. 6).

As to claim 46, the Examiner found that each member of the group agents that may be additionally added to the combination of claim 45 also relieved a side effect(s) of a ketogenic diet (Ans. 7-8). The Examiner further concluded it would have been obvious to add any one or more of these addition agents for their known and expected treatment of side effects of a ketogenic diet, e.g., selenium is known to lower serum cholesterol levels based on the teachings of Kang (Ans. 8).

C. Appellant's arguments

Appellant argues the agents of the composition used in method claim 45 "have been selected to treat side effects of a ketogenic diet because they have a synergistic effect to improve their pharmaceutical properties and, at the same time, do not interfere with the effectiveness of one another" (Br. 16)[14] when used in the particularly claimed amounts (Br. 21). Appellant also argues the Examiner has not explained why a person taking a first agent to reduce cholesterol levels would look to adding a second or third agent to also reduce cholesterol levels (Br. 23). Appellant further argues that he did not add pancreatin IX F.U. and sodium dehydrocholate to treat flatulence or cramps, but rather to treat pancreatic insufficiency and to induce low-density biliary secretion (Br. 20). Appellant challenges the Examiner's statement that a side effect of metformin is cramps as being unsupported (Br. 23-24). In short, Appellant urges that the Examiner used hindsight reconstruction and "obvious to try" combinations to arrive at the composition administered in method claim 45 (Br. 24-25).

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[14] A copy of a Declaration by Mr. Zohougbogbo, dated 16 June 2003, is said to be attached in the Appendix of Evidence to the Brief (Br. 17). However, no Declaration was attached to the Brief and the Evidence Appendix states "There is no additional material for this section" (Br. 34).

As to claim 46, Appellant again argues that the Examiner has merely selected references that teach the compounds shown in the claim without actually pointing to a suggestion or motivation to combine those references with the five agents listed in claim 45 (Br. 27).

D. Analysis

Obviousness is a conclusion of law based on underlying factual determinations. *KSR*, 127 S.Ct. at 1734; *Graham*, 383 U.S. at 17. The Examiner has provided a sufficient factual basis to conclude that it would have been *prima facie* obvious to treat known side effects of a ketogenic diet, e.g., increased serum cholesterol, with a combination of known cholesterol-lowering drugs, e.g., benfluorex, metformin, and ursodeoxycholic acid. *Kerkhoven*, 626 F.2d at 850. However, the Examiner has not provided a sufficient factual basis to conclude that it would have been *prima facie* obvious to incorporate pancreatin and sodium dehydrocholate in a cholesterol lowering composition containing metformin. Indeed, Appellant expressly challenged the Examiner's unsupported statement regarding the side effects of metformin use (Br. 23-24).

We find that Pentikainen discloses side effects were common with metformin use and that those side effects included gastrointestinal pains and meteroism (FF 7). Meteroism is defined as "tympanites; distension of the abdomen with gas" and flatulence is defined as "the presence of an excessive amount of gas in the stomach and intestines."[15] Since Pentikainen teaches that abdominal cramps (gastrointestinal pain) and flatulence (meteorism) are common side effects of taking metformin, there is a sufficient factual basis

[15] STEDMAN'S MEDICAL DICTIONARY, 20th ed., The Williams & Wilkins Company, Baltimore (1961), 590 and 931.

to conclude that it would have been *prima facie* obvious to include pancreatin and sodium dehydrocholate in a cholesterol lowering composition containing metformin.

Furthermore, the fact that the Examiner's reason for incorporating pancreatin and sodium dehydrocholate is not the same as Appellant's alternative reason is insufficient to rebut the conclusion of obviousness presented by the Examiner. *KSR*, 127 S.Ct. at 1741; *In re Dillon*, 919 F.2d 688, 693-94 (Fed. Cir. 1990). It is settled law that the teaching or suggestion to combine references' disclosures need not be explicitly stated in the prior art, but may be implicit from the state of the prior art considered as a whole. *In re Kahn*, 441 F.3d 977, 987 (Fed. Cir. 2006); cited with approval in *KSR*, 127 S.Ct. at 1741.

Thus, we conclude that, based on the totality of new factual basis above, the subject matter of claim 45 is *prima facie* obvious over the combined teachings of Marquie, Pentikainen, Poupon, Spasmo-Canulase, and Krause.

Appellant has not submitted evidence rebutting this conclusion of *prima facie* obviousness. For example, Appellant has not directed us to evidence showing that more than routine experimentation would be required to optimize the amount of benfluorex, metformin, ursodeoxycholic acid, pancreatin, and sodium dehydrocholate in the composition of claim 45. Appellant has not directed us to evidence of unpredictability, e.g., that a given cholesterol lowering agent only works on a particular patient population, or to evidence of unexpected results, e.g., synergy. *Rohm and Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997) (nothing in the rules or in jurisprudence requires the fact finder to credit unsupported

or conclusory assertions); *In re Schulze*, 346 F.2d 600, 602 (CCPA 1965) (argument in the brief does not take the place of evidence of record).

To the extent Appellant refers to the results said to be obtained by administering the composition of Example 8 of the specification (Br. 17), we note that the composition of Example 8 contains 46.1 wt. % metformin (200 mg metformin/434.4 mg total wt.; FF 3) and, therefore, is outside the claimed subject matter (claim 45 recites 36-41 wt.% metformin.[16]

Consequently, we also determine that there is sufficient factual basis to conclude that the subject matter of claim 46 is also *prima facie* obviousness. Claim 46 requires addition of at least one further enumerated agent, e.g., selenium, to the composition of claim 45. Kang discloses that selenium supplemented animals had lower serum cholesterol levels (FF 11). It is not necessary to discuss Hydrocotyle, Pondimin, or Keown for our decision. Again, Appellant has not directed us to evidence of nonobviousness of the subject matter of claim 46.

Since our decision is based upon a different factual basis, we designate it as a new ground of rejection under 37 C.F.R. § 41.50(b) to provide Appellant with an opportunity to respond to it.

IV. Order

Upon consideration of the record, and for the reasons given, it is

ORDERED that the decision of the Examiner rejecting claims 45, 47, 49, 50, 52, and 54-56 as unpatentable under 35 U.S.C. § 103(a) over the

[16] Alternatively, if sufficient excipients were added to bring the metformin wt.% into range, the wt.% of pancreatin IX F.U. in Example 8 would likely be outside the scope of claim 45.

combined teachings of Marquie, Pentikainen, Pouponin, Spasmo-Canulase and Krause is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner rejecting claims 46 and 51 as unpatentable under 35 U.S.C. § 103(a) over the combined teachings of Marquie, Pentikainen, Poupon, Spasmo-Canulase, Krause, Hydrocotyle, Kang, Pondimin, and Keown is AFFIRMED; and

FURTHER ORDERED that our decision be denominate as a NEW GROUND OF REJECTION. 37 CFR § 41.50(b).

Section 41.50(b) also provides that *WITHIN TWO MONTHS FROM THE DATE OF THE DECISION*, Appellant must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

(1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner. . . .

(2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

Should Appellant elect to prosecute further before the Examiner pursuant to 37 CFR § 41.50(b)(1), in order to preserve the right to seek review under 35 U.S.C. §§ 141 or 145 with respect to the affirmed rejection, the effective date of the affirmance is deferred until conclusion of the prosecution before the Examiner unless, as a mere incident to the limited prosecution, the affirmed rejection is overcome.

If Appellant elects prosecution before the Examiner and this does not result in allowance of the application, abandonment or a second appeal, this

case should be returned to the Board of Patent Appeals and Interferences for final action on the affirmed rejection, including any timely request for rehearing thereof.

AFFIRMED; 37 CFR § 41.50(b)

rvb

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